NAVAL HEALTH RESEARCH CENTER

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Symbols

Symbol	Definition
Tc	core temperature, generically, i.e. the influence on reflex control of skin blood flow derived from internal body temperatures
Tco	reference constant for the Tc variable in the control equation for SkBF
Tes	temperature measured in the esophagus at left atrial level
Tor	oral temperature, measured in the sublingual sulcus
Tsk	skin temperature, either of the whole body or, in combination, of a specified region
Tsko	reference constant for the Tc variable in the control equation for SkBF
SkBF	Skin blood flow
SkBFo	reference constant for the SkBF variable in the control equation
FBF	forearm blood flow
Hm	rate of metabolic heat production
Ht	rate of heat loss via the skin
C	total body heat capacity
A	coefficient of Tc in control equation
a	Tes coefficient from linear regression
B	coefficient of Tsk in control equation
b	coefficient of Tsk from linear regression
vop	venous occlusion plethysmography

SUMMARY

Problem

The design of clothing or the designation of clothing to be worn in cold environments involves understanding body temperature regulation in a "neutral zone" in which neither sweating or shivering is required to maintain thermal balance. In human calorimetry studies on near-nude male volunteers, an average T_{sk} range of 33°C to 35°C was found to bracket the neutral zone. Thermal balance, as indicated by skin temperature (T_{sk}), in this neutral zone involves control of skin blood flow (SkBF) to the area. Since this neutral zone is the optimal zone for T_{sk} of personnel operating in cold environments, it is necessary to understand how the SkBF is controlled. Once the control mechanisms have been delineated, then a mathematical model can be developed which can be used to predict the level of thermal protection needed under different environmental conditions to ensure optimal performance of personnel operating in those environments.

Objective

The objective of this study was to define the control of SkBF in the neutral zone and to develop a mathematical model based on the influence of core temperature (T_c) and T_{sk}. We hypothesized that SkBF control was similar to the control of sweating and active vasodilation and could be expressed as a linear combination of the contribution of T_c and T_{sk}.

Approach

Eight volunteers (4 male and 4 female) were instrumented for measurement of skin temperature (14 sites), esophageal temperature (T_{es}), SkBF (laser doppler flowmetry), and forearm blood flow (FBF) by venous occlusion plethysmography during trials in which T_{sk} was controlled by spraying water (at the desired temperature) over the entire body. Volunteers participated in three experimental series: (1) T_{sk} was cycled between 33°C and 35°C in a 30-min square-wave pattern with 2 15-min periods at each temperature, (2) initial and final periods of T_{sk} = 35°C separated by 1 hr at T_{sk} = 33°C, and (3) only the T_{sk} of the right forearm was cycled in the 30-min square-wave pattern. For modeling purposes, the body was treated as a single thermal

compartment from which heat is lost convectively. The linear relationship of T_{sk} and T_c for the control of SkBF were described by the equation:

$$SkBF - SkBF_o = A \bullet (T_c - T_{co}) + B \bullet (T_{sk} - T_{sko})$$

with the constants (A, B, T_{co}, T_{sko}) being determined from the experimental data.

Results

When T_{sk} was cycled between 33°C and 35°C in a 15 min square-wave pattern, FBF responded in a similar pattern. T_c followed an inverse pattern to the change in T_{sk}. Changes in T_c developed over a longer time period. When T_{sk} was held constant at 33°C for an hour, T_c and FBF responded to T_{sk} transitions in a pattern similar to the square-wave changes with T_c reaching a plateau (total increase = 0.13°C) after 10 minutes. When T_{sk} was returned to 35°C, FBF increased quickly, and T_c decreased. With a 2°C change in T_{sk}, FBF changed ~0.8 ml•100ml^{-1}•min^{-1} in both directions. Cycling of the T_{sk} in the right forearm produced no change in FBF. When the data was fitted to the linear equation model:

$$FBF = aT_{es} + bT_{sk} + K$$

it was determined that most of the variance of FBF could be accounted for by T_{sk}. Using the linear equation model described in the methods section, the inverse relationship of T_c and T_{sk} in the control of SkBF was predicted.

Conclusion

The data reveals that the reflex influence of skin temperature on SkBF dominates control of thermal balance in the 33°C to 35°C range of skin temperatures. The immediate change in SkBF that occurs in reflex response to a change in skin temperature results in slight overcompensation in thermal balance. Consequently, core temperature subsequently moves in the opposite direction, increasing when skin temperature falls and vice versa. A new equilibrium core temperature is established when the resultant feedback influence of core temperature on SkBF corrects the thermal balance.

INTRODUCTION

Control of skin blood flow (SkBF) suffices for control of body temperature regulation in humans except when sweating or shivering are required. We speak of a "neutral zone" or "vasomotor zone" of thermoregulation that separates a zone of metabolic regulation, where shivering is evoked in defense against cooling; and a zone of active vasodilation and sweating in which these effectors are called upon for dissipation of heat (Burton 1941; Burton & Bazett, 1936; DuBois, 1939; Hardy, 1961). The constancy of the rhythm of body temperature over long periods during the day and night when activity is mild or nil and clothing is selected to minimize environmental thermal stress testifies to the effectiveness of the control of cutaneous vasomotor state in balancing body heat production with heat loss to the environment.

The regulatory range of SkBF within the neutral zone appears small when viewed in terms of forearm blood flow (FBF), the usual measure that has been employed in quantitative analysis of control of SkBF in the range of active vasodilation. FBF may range from a minimum near 2 $ml \cdot min^{-1} \cdot 100ml^{-1}$ in a subject who is cool and, in the course of subsequent warming, reach only 5 or 6 $ml \cdot min^{-1} \cdot 100ml^{-1}$ before the clear onset of sweating and active vasodilation that can bring FBF above 20 $ml \cdot min^{-1} \cdot 100ml^{-1}$ (Love & Shanks, 1962; Taylor et al., 1984; Wyss et al., 1974; Wyss et al., 1975). These changes in FBF are due to changes in SkBF in conditions where blood flow remains constant in underlying muscle.

The FBF range of 2 to 6, say, seems minor compared to the potential for 20 $ml \cdot min^{-1} \cdot 100ml^{-1}$. However, seen in terms of the actual changes in SkBF, the potential for altering thermal balance becomes evident. At minimal FBF, SkBF is, presumably, at the minimum necessary for supply of the oxygen uptake of the skin, probably less than 2 $ml \cdot min^{-1}$ per 100 ml of skin (Cooper et al. stated that SkBF could reach zero). If FBF increases 4 $ml \cdot min^{-1} \cdot 100ml^{-1}$ by virtue of increase in SkBF, then SkBF in terms of flow per unit volume of skin increases by 4 $ml \cdot min^{-1}$ times the ratio of skin volume to limb volume, i.e., at least 10 (Cooper, 1955). According to this crude estimate, the ratio of maximum and minimum SkBF within the neutral zone is 20:1 or more; much more according to Cooper et al. This ratio also estimates the

associated ratio of maximum and minimum rates of convective heat transfer from the body interior to the skin surface, given constant skin (Tsk) and core (Tc) temperatures and the assumption that convective heat transfer to the body surface is in direct proportion to SkBF times the difference between Tc and Tsk.

A hint of the potential of changes in SkBF associated with changes in FBF that are small on a full scale of 20 $ml \cdot min^{-1} \cdot 100ml^{-1}$ is given by the rapid changes in body temperature that occur when non-thermal factors interfere with the control of SkBF, e.g., the decline after administration of anesthesia (Sessler et al., 1991), and the increase on assuming the upright posture (Nielsen et al., 1939). Also, when Tsk was increased to rewarm hypothermic subjects, they responded with a decrease in esophageal temperature (Tes) in the next few minutes, associated with FBF levels near 3 $ml \cdot min^{-1} \cdot 100ml^{-1}$ (Savard et al., 1985). We presume the marked increase in convective distribution of heat from the body core during the "afterdrop" in Tes was due to slight increase in SkBF relative to the minimum level that existed just previous to rewarming.

What are the limits of the neutral zone? Expressed as environmental temperatures, the zone spans extreme arctic conditions to mild warm conditions given appropriate clothing. But the end result of the interaction between environment, clothing and body heat production is Tsk. According to calorimetric studies with near-nude male subjects, average Tsk of 33°C and 35°C bracket the neutral zone (Burton 1941; Hardy, 1961; Hardy & DuBois, 1938). In Craig and Dvorak's studies of body temperature in males immersed in water held at constant temperature, the range appeared to be narrower, only 35°C to 35.5°C (Craig & Dvorak, 1966).

Our interest in neutral zone thermoregulation focused on the control scheme of regulation of SkBF in this zone. Although SkBF control has been analyzed quantitatively, these were studies in which men were made hyperthermic and reached high levels of Tsk and FBF (Johnson et al., 1974; Wenger et al., 1975; Wyss et al., 1974, Wyss et al., 1975). Control in the neutral zone has not been investigated, perhaps because the changes in FBF are small compared to the sensitivity of venous occlusion plethysmography (vop). We felt that technological advances in

our vop system would afford sufficient resolution. Our hypothesis was that SkBF control would be similar to control of sweating and active vasodilation and therefore could be expressed as a linear combination of influences from Tc (recorded from the esophagus) and Tsk (maintained uniform over the body surface by a deluge of water). We also developed a model with SkBF control simulated according to this linear combination and heat transfer simulated as simple convective cooling via the skin. The model predicted and the experimental studies revealed that the equilibrium level of Tc varies inversely with Tsk within the neutral zone.

METHODS

Four women and four men were subjects for this study. Mean age, height and weight were 40 (26 to 58) yr, 169.1 (155 to 187) cm, and 63.1 (50.9 to 100) kg. Informed consent was obtained according to procedures and guidelines set by the Human Subjects Review Committee of the University of Washington.

Subjects participated in three different experimental series; one in which Tsk was cycled between 33°C and 35°C in a square wave pattern with two 30-min cycles, one in which initial and final periods with Tsk at 35°C were separated by an hour with Tsk at 33°C, and one in which only the temperature of the skin of the right forearm was cycled in the 33°C to 35°C square wave pattern. The order for each subject was randomized. In addition, we extended the whole-body Tsk cycling experiments on 2 subjects, adding a 10-min period with Tsk near 42°C to elevate Tes, followed by a repetition of the Tsk cycles between 33°C and 35°C.

Control of whole-body Tsk was accomplished by means of a deluge of water sprinkled from irrigation nozzles arrayed above and below the subjects who reclined supine on open nylon mesh stretched on a metal frame. Water was sprayed over the entire body except the head and neck and, sometimes, one arm, which were exposed to room air. Foam rubber blankets were wrapped around the spray nozzle framework, enclosing the subject in an insulating cocoon. For details of the Tsk control system, see Brengelmann et al. 1994. The subjects were dressed in lightweight polypropylene underwear to enhance uniform distribution of water over the skin.

In the experiments in which only the temperature of the skin of one forearm was controlled, water was sprayed over the forearm from a separate set of nozzles enclosed within a plastic drape (Savage & Brengelmann, 1994). The subjects reclined on the same mesh and wore light cotton surgical garments.

Tsk was recorded from thermocouples imbedded in copper disks the size of a penny taped to the skin at 14 points distributed over the body. The standard deviation from the mean of these was 0.6°C during the transition from one water temperature to another and fell to 0.4°C within 5 min. Tsk of the arm exposed to room temperature averaged 31.22 ± 0.11°C.

Tes was recorded from a thermistor at the end of a 1mm diameter catheter swallowed to the level of the left atrium according to the characteristic biphasic shape of the atrial waveform in the electrocardiogram from a unipolar electrode adjacent to the thermistor (Brengelmann et al, 1994). The positioning of the probe took place after the subject was supine. A small suction tube was placed in the mouth for saliva removal.

Oral temperature was recorded in the experiments in which only forearm Tsk was controlled. A thermocouple was placed in the sublingual sulcus and the subjects were asked to keep their mouths closed throughout the experiment.

FBF was measured by vop (Savage & Brengelmann, 1994; Whitney, 1953). FBF was recorded in 5-min cycles during which circulation to the hand was arrested by an arterial cuff inflated to 200 mmHg for 4 min. The venous occlusion cuff was inflated to 5 mmHg below diastolic blood pressure for 15 of every 30 sec during the 4-min periods of wrist occlusion. The circumference gauges were placed midway between the olecranon and styloid processes at the same location for each experiment.

An indication of SkBF was obtained through laser Doppler flowmetry using the Laserflo blood perfusion monitor (TSI Model BPM 403). The small probe (TSI Model BPM403 - 8 mm

diameter) was placed about 1 or 2 cm distal to the circumference gauge and attached to the skin with surgical tape.

With the exception of FBF, data were recorded digitally at 1-sec intervals. These records were smoothed by a digital simulation of a low-pass filter with a 10-sec time constant and represented by every fifteenth point, i.e., the sample rate in the smoothed records we worked with was $4 \cdot min^{-1}$. During venous occlusion, forearm circumference was recorded digitally at 20 $samples \cdot sec^{-1}$. FBF was calculated from the slopes of the circumference records, obtained as the linear regression of the data in a segment of the record marked by cursors placed manually to bracket the region between initial cuff artifact and final rolloff (Savage & Brengelmann, 1994).

Eight subjects (identified as A through H) participated in the experiments with Tsk cycles. After 10 min with Tsk constant at 35°C, Tsk was set at 33°C and 35°C for 15 min each, in two 30-min cycles. FBF was recorded in both arms. The right arm was sprayed, but the left arm was outside the cocoon exposed to room air. We refer to these, respectively as the "wet" and "dry" arms. G and H were the subjects of the experiments with two sequences of Tsk cycles separated by a period of heating

Seven subjects (all except Subject C) participated in the experiments in which, after an initial 10 min at 35°C, Tsk was held constant at 33°C for 1 hr and then elevated to 35°C for the final 10 min. As in the studies with Tsk cycles, the head and neck were exposed to room temperature. FBF was measured only in the right forearm which was sprayed. The left arm was inside the cocoon and thus also sprayed.

Seven subjects (A through G) completed the experiments in which the temperature of only the right forearm was controlled in the square wave pattern described above.

Model

In order to explore the interaction between the reflex effects of Tsk changes and the thermal consequences, we employed a simple model built from the following relationships. The

body is treated as a single thermal compartment from which heat is lost convectively. The core compartment is at uniform temperature, Tc, with total-body heat capacity (C) (kcal·°C^{-1}). Heat is produced in this compartment at rate Hm (kcal·min-1). Heat is lost from this compartment at the rate Ht (kcal·min^{-1}). The relationship between these is (the dot over Tc indicates time rate of change)

$$1.\ C\cdot\dot{T}c=(Hm - Ht)$$

Heat loss is modeled after Burton's thermal circulation index (Burton, 1934), i.e., as the product of SkBF times the difference between Tsk and Tc. This elementary treatment of the convective distribution of heat in the body states that all heat lost from the body is delivered to the body surface by blood that arrives at the skin at Tc and leaves equilibrated with Tsk. Respiratory heat loss can be ignored for the purposes of these analyses since it can simply be deducted from heat production, i.e., Ht is non-respiratory heat loss and balances against Hm minus respiratory heat loss.

$$2.\ Ht = SkBF\cdot k\cdot (Tc-Tsk)$$

In this representation, k is the heat capacity of blood, for simplicity taken as 1.0 kcal·°C^{-1} per liter of blood, Tsk is taken as uniform over the entire body, and SkBF is the total blood flow through skin, in liters·min^{-1}.

Finally, the control of SkBF is based on a linear combination of Tc and Tsk, after the descriptions by Wyss et al. 1974, 1975 and Wenger et al. 1975:

$$3.\ SkBF - SkBFo = A\cdot (Tc - Tco) + B\cdot(Tsk - Tsko)$$

The terms subtracted from SkBF, Tc, and Tsk, with the "o" appended represent constants, the reference levels for the respective variables.

These relationships were connected with the aid of the Tutsim simulation language (Tutsim Products, Palo Alto, CA) as represented in the block diagram in Figure 1. The output of block 9 is Tc, obtained as the integral of the difference between Hm and Ht divided by C (rearrangement of equation 1). Box 7 forms the difference between Hm, set constant at 1.5 kcal/min, and Ht, computed in box 6 as the product of SkBF and (Tc-Tsk), implementing equation 2 with k=1. Box 8 multiplies the output of box 7 by 1/C. The summation in block 4 that forms (Tc-Tsk) is fed Tc from the output of block 9 and Tsk as whatever waveform is desired for a particular simulation. The implementation of the control equation, equation 3, is through the summation performed in box 3 of inputs supplied via boxes 1 and 2. These multiply their inputs by the constants A and B, respectively, and incorporate the constants Tco and Tsko as negative inputs so that the A and B multiply the difference between the input variable and the respective reference constant. Box 5 supplies the constant SkBFo and also sets a lower limit on SkBF of SkBFo, taken as zero in our simulations.

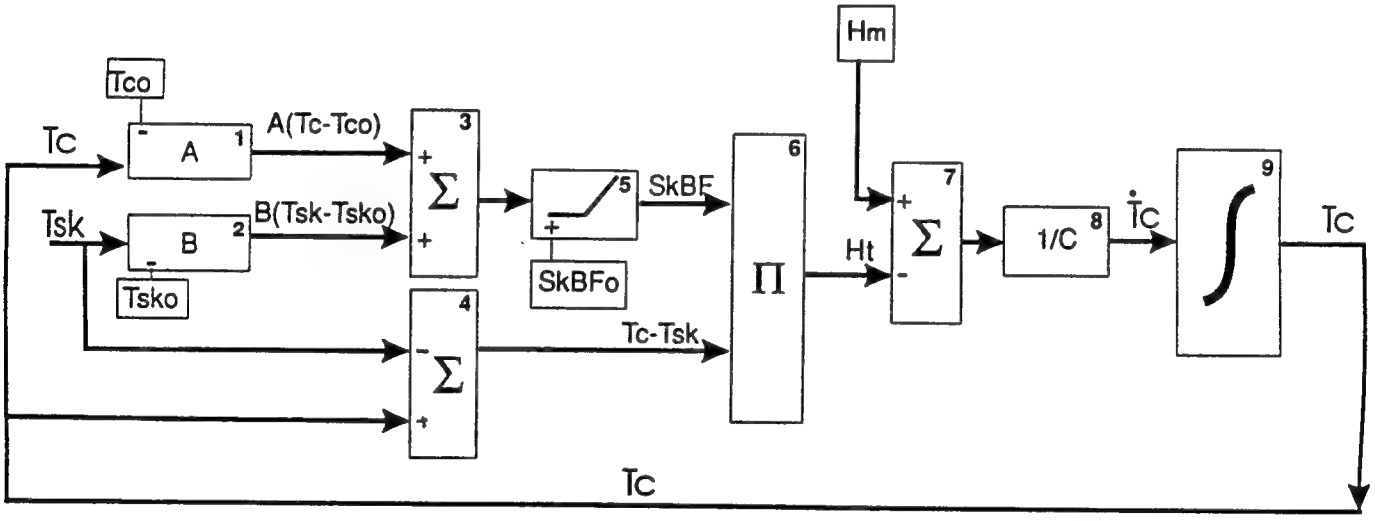

Figure 1: Block diagram of model incorporating a single thermal compartment and control of SkBF via a linear combination of Tc and Tsk. Reference constants Tco and Tsko are subtracted from their corresponding variables and the differences multiplied by A and B, respectively in boxes 1 and 2. Boxes labeled with capital greek sigma form the algebraic sum of their inputs (algebraic sense indicated by plus and minus signs at the inputs), box labeled with capital greek pi forms the product of its inputs. Box 5 passes either the output of box 3 plus SkBFo or SkBFo, whichever is greater. Box 9 integrates the output of box 8.

Analysis

We analyzed our data with linear regressions using the Excel™ spreadsheet program (Microsoft Corp). For each time in the sequence of samples of FBF, an average was computed from the data from the individual subjects. Associated values for Tes and Tsk for a given FBF time were the averages of the individual values obtained at that time. Parameters from these regressions that are mentioned in the text are expressed 95% confidence limits.

Also, to compare Tes data from the beginning versus the end of the experiments, we averaged the Tes data from the 5 to 10 min segment and from the last 5 min of the experiment for each subject and treated these two averages as paired values. These were compared by paired t-test and are expressed ± SD.

RESULTS

When we cycled Tsk between 33°C and 35°C, FBF responded in a pattern similar to the Tsk square wave. Tes followed a roughly inverse pattern, rising approximately 0.1°C after Tsk fell, and vice versa. Data from a typical experiment are shown in Figure 2. The rapidity of the FBF response to changes in Tsk is illustrated in Figure 3. The slopes of the record of forearm circumference during venous occlusion were obviously reduced within 1 min after a downward change in Tsk was initiated and appeared to stabilize at a new level as quickly as Tsk did. Changes in Tes developed over longer periods. Laser-Doppler flowmetry also reflected the pattern of Tsk, particularly in records obtained from the dry arm. Records from the wet arm were erratic, presumably due to interference from the continuous water spray. Nonetheless, the pattern of prompt response to Tsk change could often be discerned.

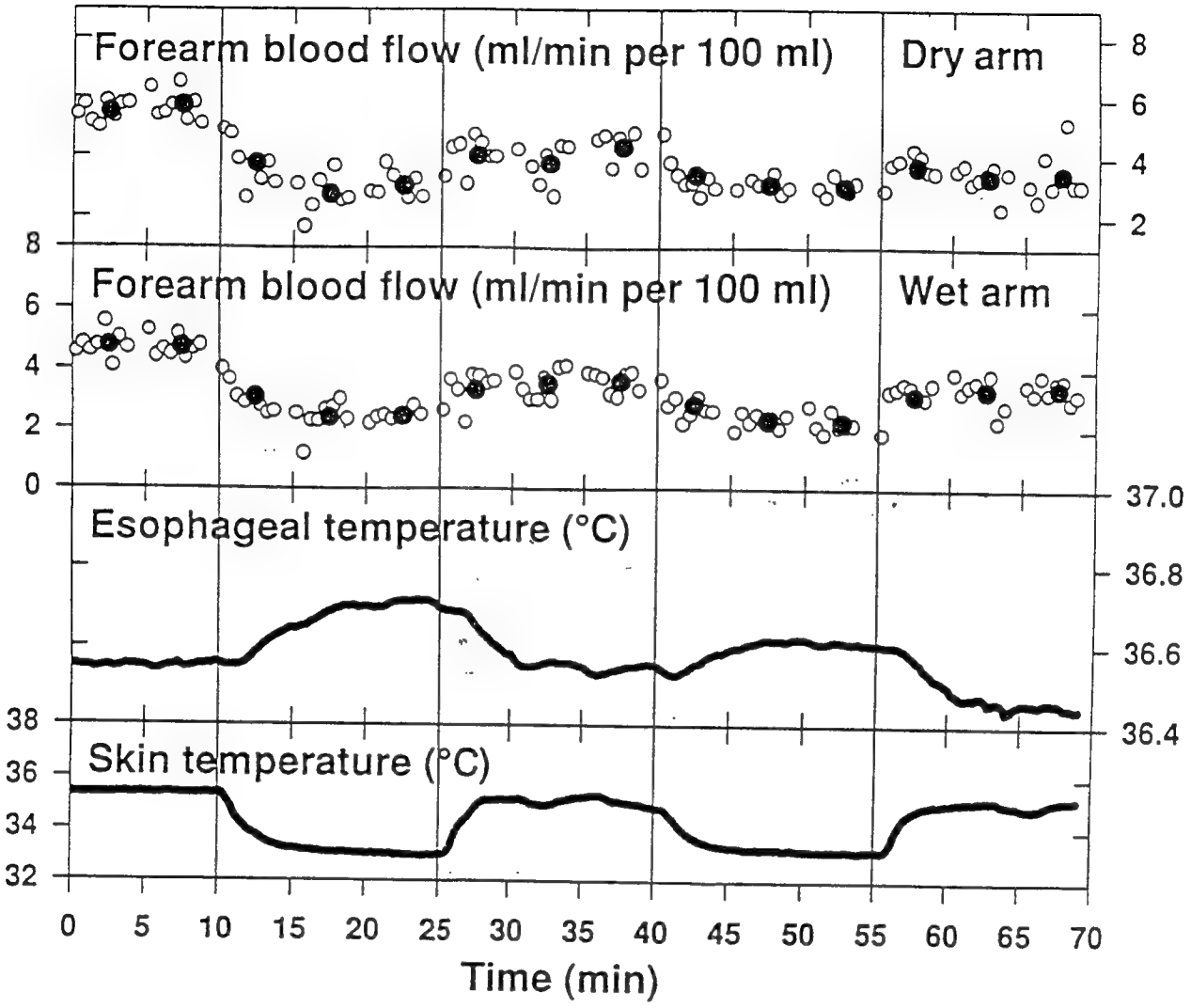

Figure 2: Typical results of experiments with square wave Tsk, data from subject C. FBF (ml(100ml$min)^{-1}$) followed Tsk in both the arm in which temperature was cycled with the whole body (wet arm) and in the arm exposed to room air (dry arm). Open circles, FBF data obtained every 30 sec for 4 min out of each 5 min. Closed circles, 4-min averages of batches of FBF data. The inverse relationship between Tsk and Tes was observed in all 8 subjects.

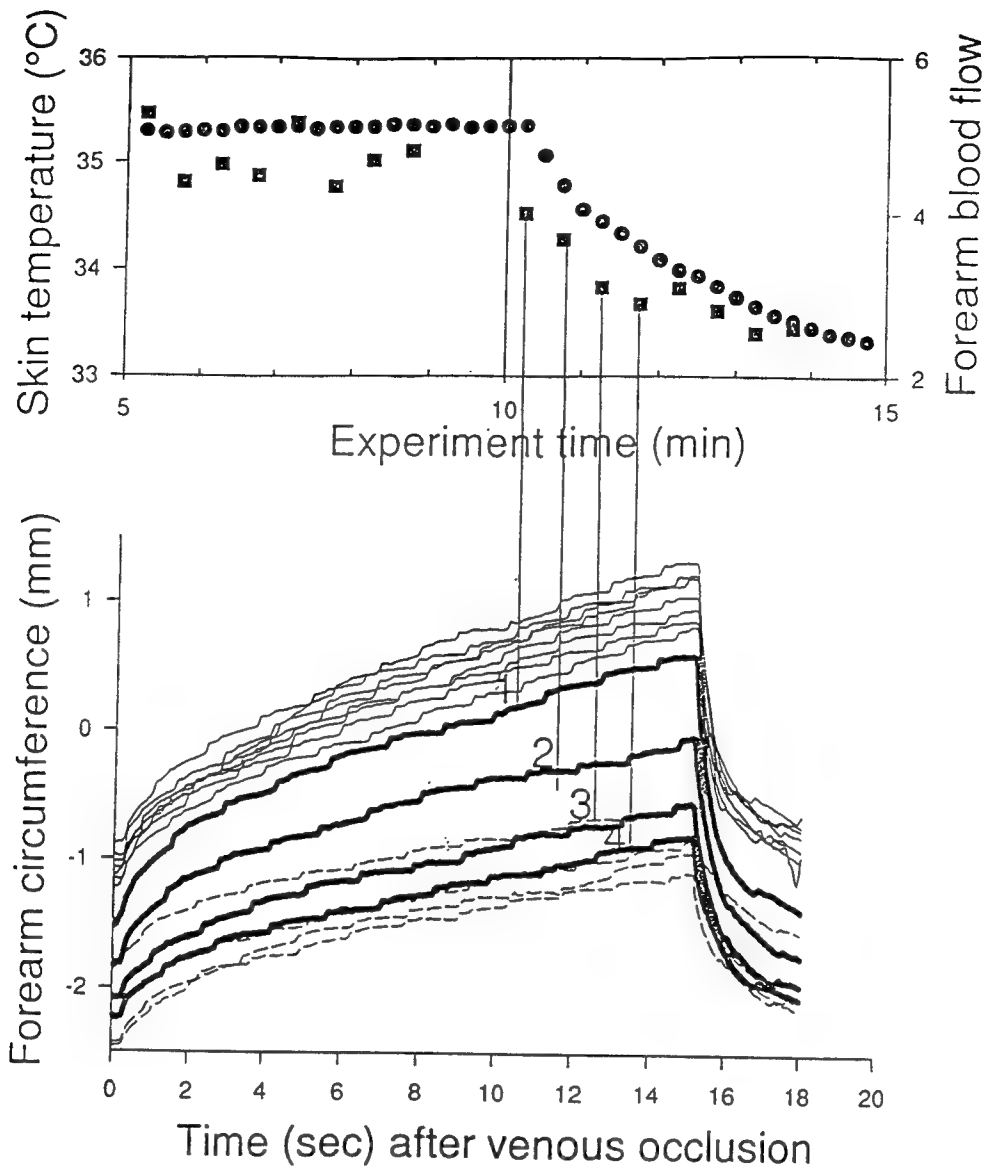

Figure 3: Rapid FBF response to skin temperature. Upper panel, 10 min of data from Figure 2: filled circles, average Tsk, filled squares, FBF. Water temperature in the spray system was set to 33°C at 10 min. Lower panel, two series of records of forearm circumference taken at half minute intervals from 5.5 to 9 min and from 10.5 to 14 min, i.e., one for each of the FBF data points in the upper panel. The scale is in units of mm relative to the circumference at which tension in the circumference gauge was 15g. Forearm venous outflow was occluded for 15 sec for each record. The circumference records obtained during the segment between 5.5 and 9 min are the uppermost ones, drawn as thin lines. The eight data points for forearm blood flow in the upper panel are calculated from the slopes of the linear portions of these records. The circumference records drawn as heavy lines and numbered in sequence are the first collected after the change in water temperature began. They are connected by vertical lines to the corresponding data points in the upper panel. The remaining four circumference records are drawn as thin dashed lines clustered around records labeled "3" and "4".

The characteristics of the responses shown in Figure 2 were exhibited by all 8 subjects. Averaged data are shown in Figure 4. The two degree changes in Tsk caused changes in FBF and Tes of approximately 1 $ml \cdot min^{-1} \cdot 100ml^{-1}$ and 0.11°C, respectively. FBF levels in the wet arm were higher, on the average (difference in overall means 0.7 ± 0.4 $ml \cdot min^{-1} \cdot 100ml^{-1}$, $p < 10^{-21}$). Although the Tes record in Figure 4 shows a downward trend (0.05°C, insignificant by paired t-test), individuals varied: 3 showed a slight decline, 4 a slight increase and 1 no change during the 70-min experiment.

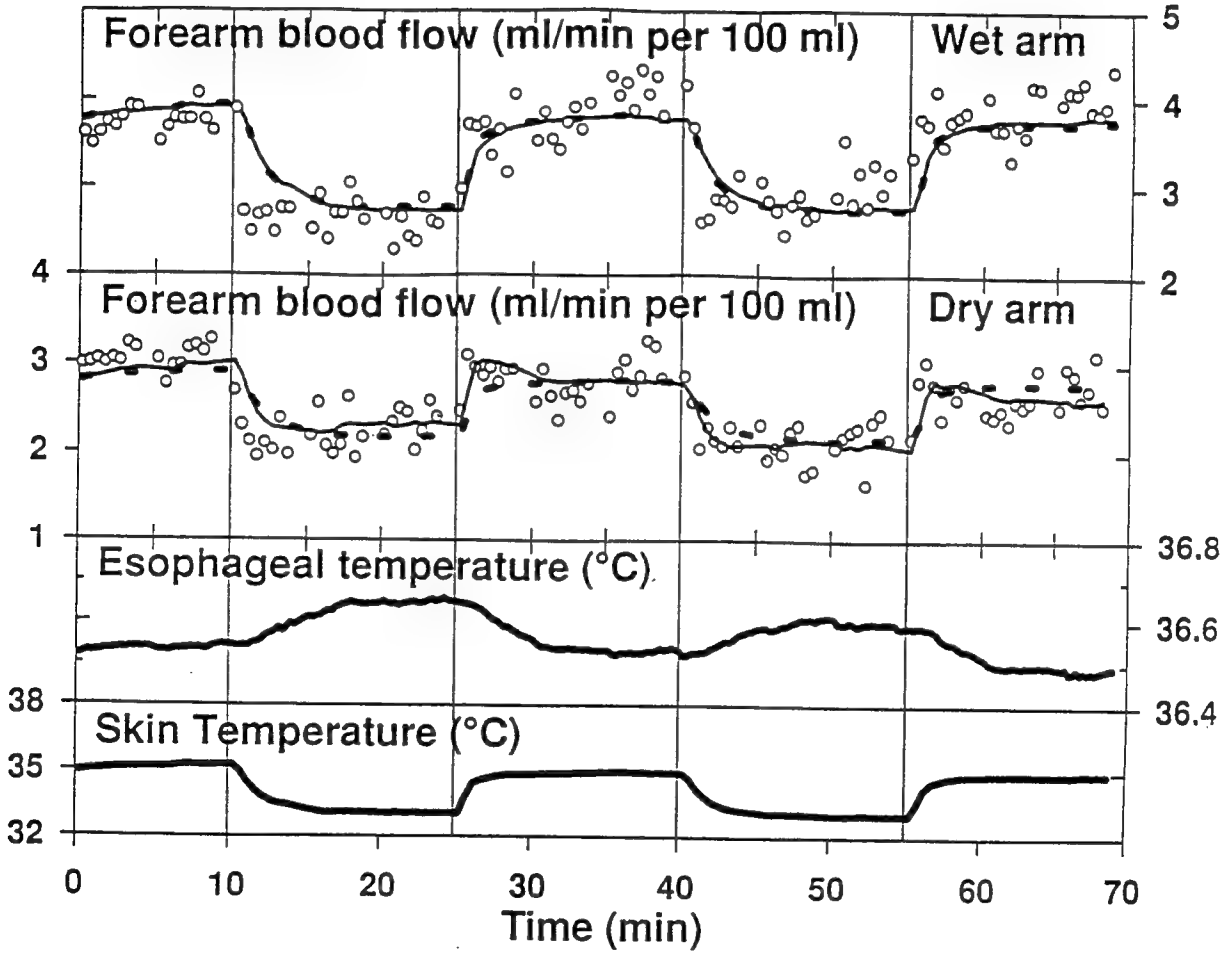

Figure 4: Data from square wave experiments from 8 subjects averaged together. FBF data are overlaid with lines predicted from linear regressions: the solid lines from regressions on Tes and Tsk; the dashed lines, from regression of FBF on Tsk only.

In the double length square wave experiments on Subjects G and H, Tes rose rapidly when water temperature was elevated to 42°C after the first series of Tsk cycles. FBF in both the dry and wet arms followed Tes. Then Tsk was set at 33°C. Dry arm FBF fell rapidly and Tes, somewhat slower. Both reached levels previously associated with Tsk at 33°C within 15 min. Thereafter, these records were nearly indistinguishable from data from the first series of Tsk cycles (Figure 5). In the wet arm, the recovery of FBF was much slower, but eventually also retraced previous values.

In the experiments in which Tsk was held at 33°C for an hour, the Tes and FBF responses to the Tsk transitions were similar to those observed in the square wave experiments. About 10 min after Tsk was set at 33°C, Tes reached a plateau after a total increase of approximately 0.13°C. During the remainder of the 60 min of constant Tsk, Tes generally fell slightly. The slope of the linear regression of Tes against time over the period from 26 min to 70 min for the averaged data in Figure 6 is $-0.002°C \cdot min^{-1}$, amounting to a total of 0.09°C. When Tsk was driven back to 35°C, FBF rose promptly and Tes fell in all subjects. Tes, on the average, appeared slightly lower at the end of the experiment (0.06°C) compared to the beginning, but this difference was insignificant ($p=0.27$). Again subjects varied in their overall Tes responses: four showing a slight decline and three a slight increase. The change in FBF accompanying the changes in Tsk was approximately 0.8 $ml \cdot min^{-1} \cdot 100ml^{-1}$ when Tsk was raised or lowered.

FBF remained nearly constant in all of the experiments in which Tsk of one forearm was cycled between 35°C and 33°C; individual responses closely resembled the averaged data shown in Figure 7. Oral temperature was not significantly different at the end of the experiment, compared to the beginning ($p=0.42$).

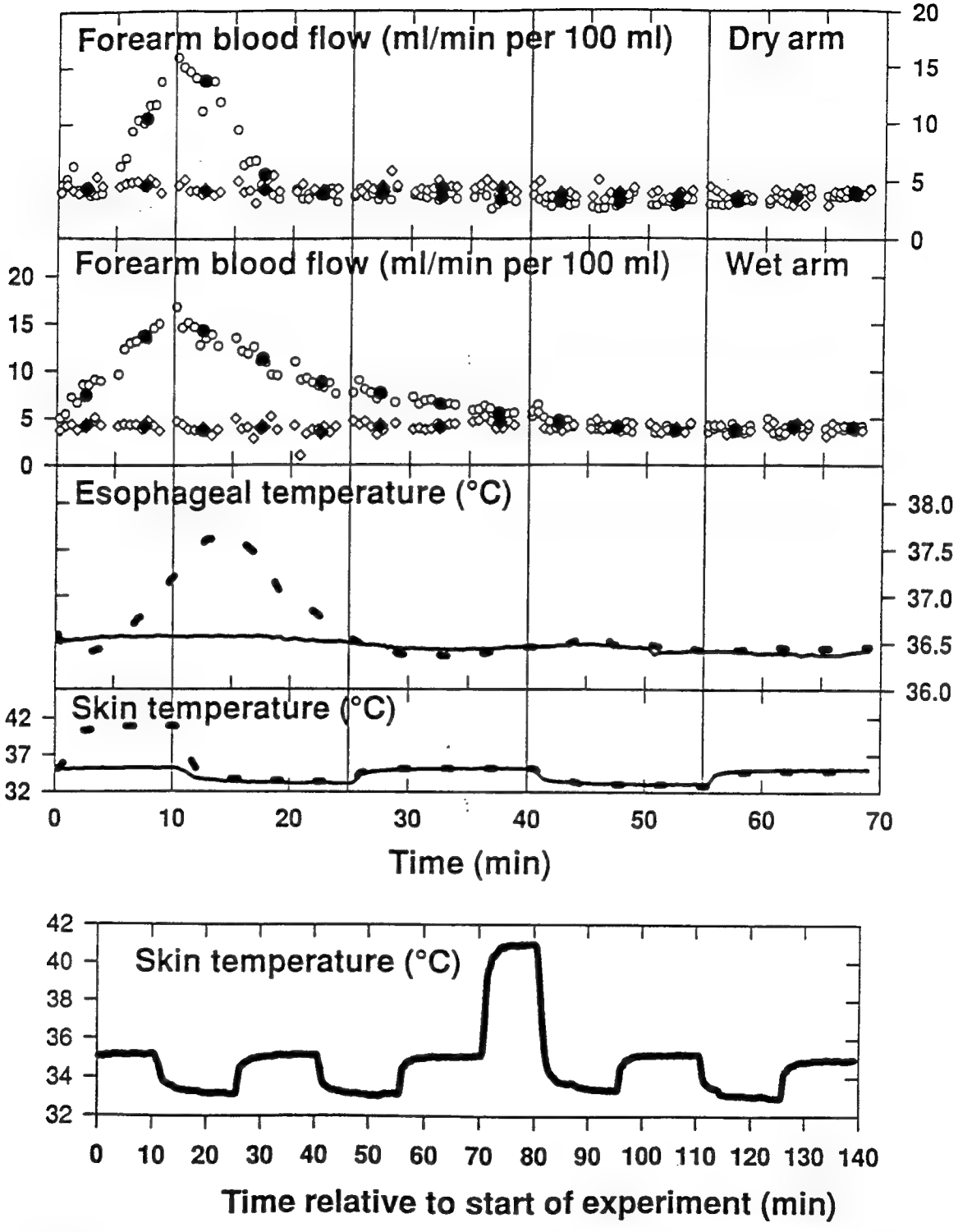

Figure 5: Averaged data from 7 subjects of experiments with Tsk held at 33°C for 1 hr. FBF data are overlaid with (nearly identical) lines predicted from linear regressions; solid on Tes and Tsk, dashed on Tsk only.

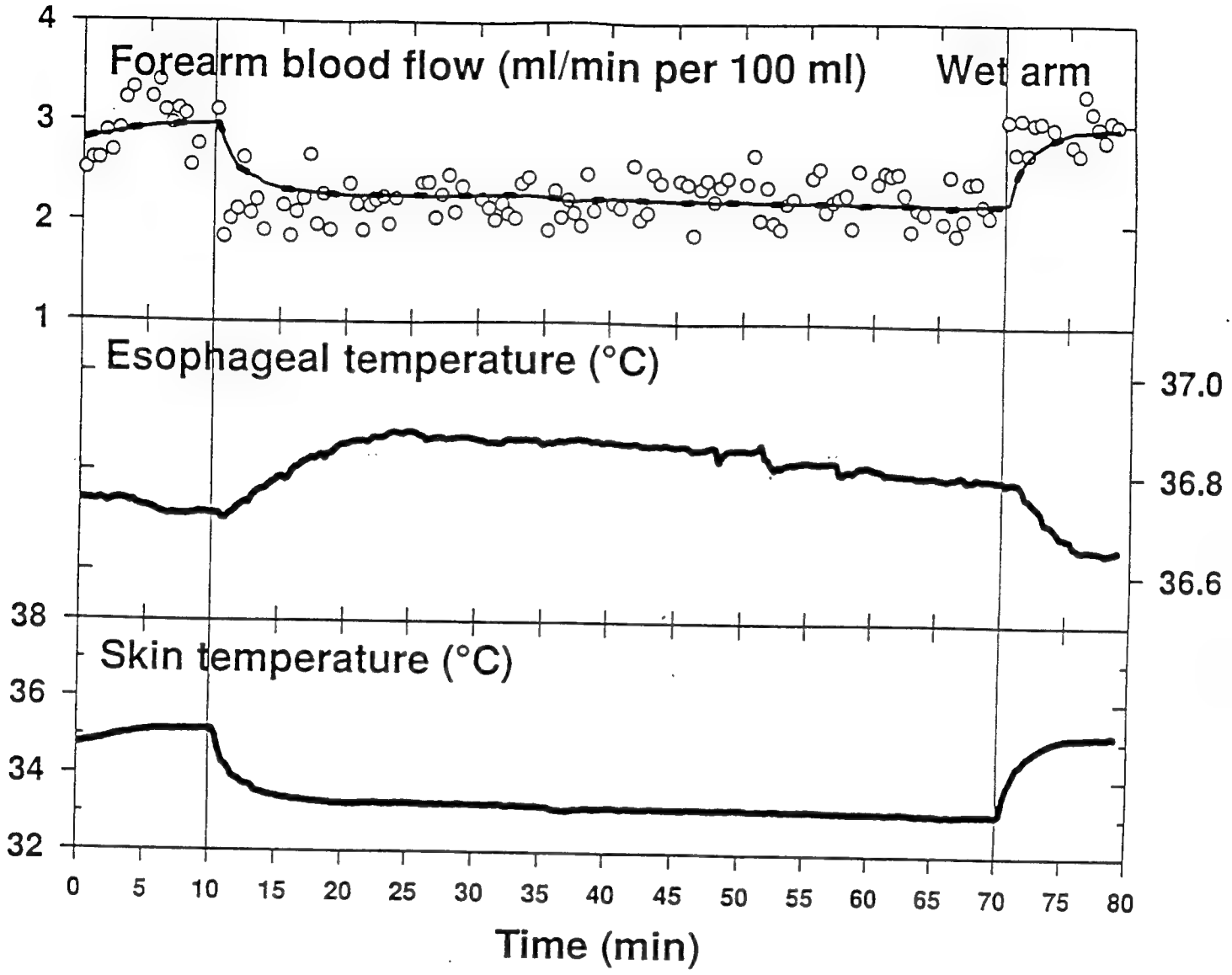

Figure 6: Averaged data from 7 subjects of experiments in which the temperature of only the right forearm was cycled. Solid line in FBF panel is prediction of regression on Tsk only.

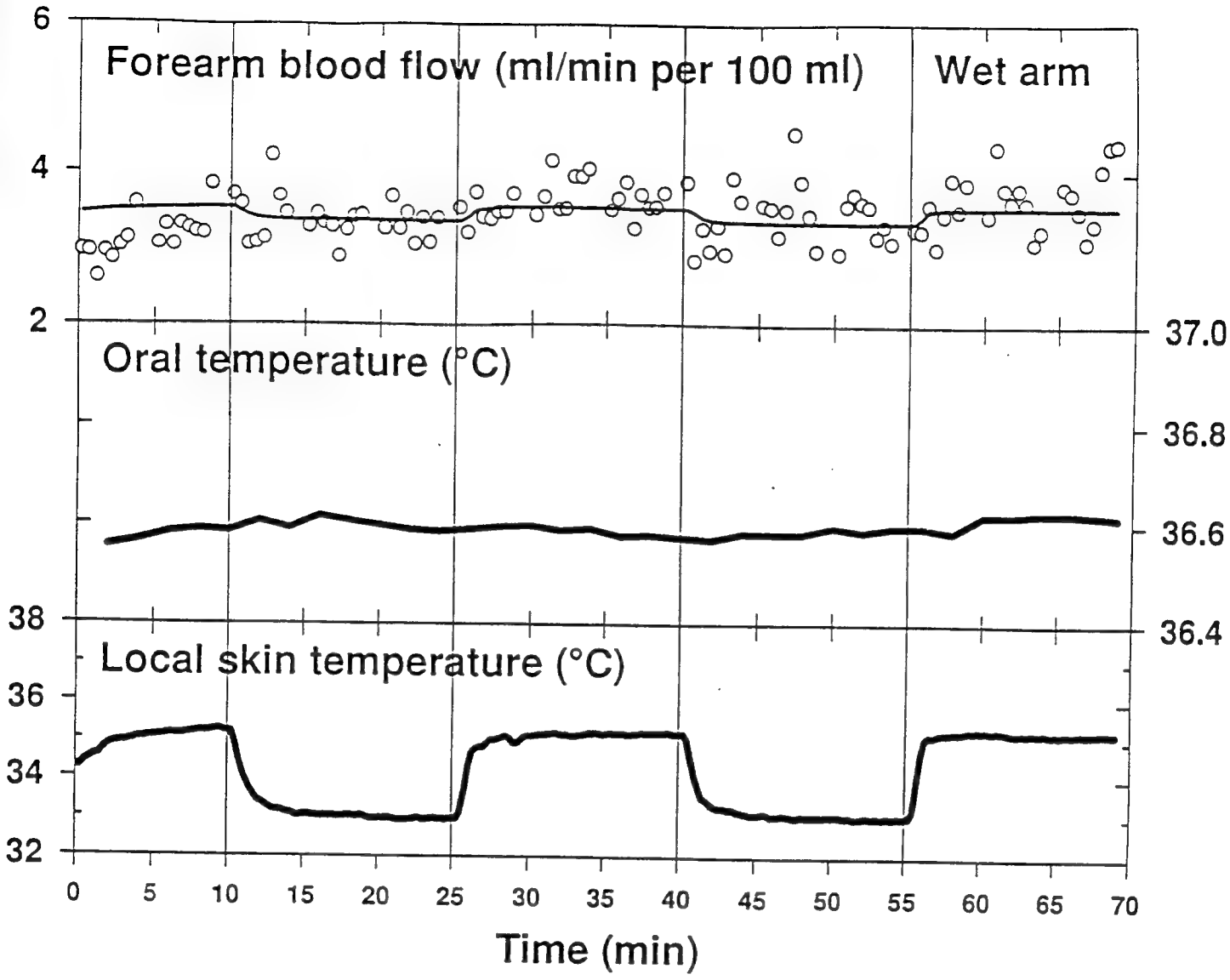

Figure 7: Data from subject H in whom Tsk was cycled between 35°C and 33°C as in experiments shown in Figures and followed by elevation of water temperature to 42°C for 10 min and repetition of the Tsk cycling. Lower panel shows Tsk for the entire 140 min. In the upper panels, data from the first and second 70-min periods are superimposed. Open and closed symbols are individual FBF points and 4-min averages, respectively, diamonds from the first 70 min; circles from the second 70 min. For Tes and Tsk, data from the first 70 min are shown as solid lines, the last 70 min as dashed lines.

Data Analysis

We fitted our data to the following linear equation, similar in form to the previously described (Wenger et al., 1975; Wyss et al., 1974, Wyss et al., 1975) quantitative model of the control of SkBF expressed by Equation 3 (methods section):

$$FBF = aTes + bTsk + K.$$

The predictions appear as solid lines overlaying the FBF data in Figures 4 and 6. We also calculated regressions on Tsk only; predictions are plotted as dashed lines (Figures 4 and 6). Parameters and statistics from the regressions are listed in Table 1.

Table 1

				Sum of squares		
Regression on	a*	b*	R	Total	Residual	Mean
Whole body Tsk cycled between 33°C and 35°C (n=8)						
Tes, Tsk (wet arm)	-1.21.16, $p = 0.3$	0.480.12, $p < 10^{-11}$	0.81	36.2	12.6	0.12
Tsk only (wet arm)		0.530.07, $p < 10^{-26}$	0.81	36.2	12.7	0.12
Tes, Tsk (dry arm)	4.01.6, $p < 10^{-5}$	0.520.09, $p < 10^{-19}$	0.78	18.1	7.1	0.07
Tsk only (dry arm)		0.340.06, $p < 10^{-18}$	0.72	18.1	8.6	0.08
Two periods of 35°C separated by 1 hr at 33°C (n=7)						
Tes, Tsk (wet arm)	0.131.48, $p = 0.9$	0.380.12, $p < 10^{-8}$	0.73	18.8	8.7	0.07
Tsk only (wet arm)		0.370.06, $p < 10^{-21}$	0.73	18.8	8.7	0.07
Cycling of forearm Tsk only (n=7)						
Tsk only (wet arm)		0.090.07, $p = 0.02$	0.23	15.3	14.5	0.13
Double length experiment, Subject G						
Tes, Tsk (wet arm)	8.130.99, $p<10^{-38}$	0.630.11, $p<10^{-22}$	0.67	1989.5	664.2	3.24
Tes, Tsk (dry arm)	1.960.57, $p<10^{-10}$	0.300.06, $p<10^{-10}$	0.41	393.3	231.2	1.12
Double length experiment, Subject H						
Tes, Tsk (wet arm)	8.050.60, $p<10^{-69}$	0.680.09, $p<10^{-34}$	0.83	1934.1	326.8	1.50
Tes, Tsk (dry arm)	6.150.53, $p<10^{-59}$	0.500.08, $p<10^{-26}$	0.79	1179.5	253.0	1.16

* ± 95% confidence limits

For the data from the experiments with Tsk cycles, slight differences in the predictions are apparent for the dry arm, but not for the wet arm. In both arms, Tsk accounted for most of the variance in FBF. Note that the coefficient for Tes for the wet arm is negative. Though positive, the Tes coefficient for the dry arm is low compared to values (roughly 10 $ml \cdot min^{-1} \cdot 100ml^{-1}$ per°C) previously published (Johnson et al., 1974, Wenger et al., 1975, Wyss et al., 1974, Wyss et al., 1975).

For comparisons of data from the wet arm versus the dry arm, we experimented with various combinations of dummy variables. We pooled together the wet arm and dry arm data, and used three dummy variables, the first equal to zero for the wet arm and one for the dry arm data, and the second and third equal to zero for the wet arm data and, respectively, Tes and Tsk for the dry arm data. The results of this regression simply duplicate the two individual regressions on Tes and Tsk for the wet and the dry arm (solid lines in Figure 4) with the parameters for the dummy variables amounting to corrections to the intercept and the coefficients for Tes and Tsk for the wet arm to obtain the corresponding parameters for the dry arm, except that significance of the corrections can be calculated. The p value for the dummy variable corresponding to the correction to the Tes coefficient, 5.12, was less than 0.0002. The Tsk coefficient correction of 0.03 was insignificant ($p = 0.6$). The p value for the correction in intercept was also insignificant (0.4). But, when we simplified the dummy variable analysis to include Tes and Tsk and only one dummy variable (zero for the wet arm data, one for the dry arm data) so that only the intercept was corrected for the wet versus dry arm data, the deterioration of the fit was minor, increasing the mean residual sum of squares from 0.09 to 0.10 $ml \cdot min^{-1} \cdot 100ml^{-1}$. According to this simple analysis, the dry arm data are offset downward by 0.80.1 $ml \cdot min^{-1} \cdot 100ml^{-1}$ ($p<10^{-48}$) and therefore we view the difference as simply the difference in mean values mentioned above.

Regressions on Tes and Tsk of the FBF data obtained in the double-length experiments (Figure 5) yielded similar Tsk coefficients and much higher and highly significant Tes coefficients reflecting the obviously powerful role of Tc in driving SkBF (Table 1).

Regression analysis of wet arm FBF data from the 7 experiments in which Tsk was held at 33°C for an hour yielded a Tsk coefficient near 0.4 $ml \cdot min^{-1} \cdot 100ml^{-1} \cdot °C^{-1}$ (Table 1). Incorporation of Tes in the regression did not reduce the residual mean sum of squares and yielded a coefficient not significantly different from zero (Figure 6).

A slight locally mediated influence of Tsk, less than 0.1 $ml \cdot min^{-1} \cdot 100ml^{-1} \cdot °C^{-1}$, is indicated by the regression on local Tsk of the FBF data obtained when the temperature of only one forearm was cycled between 33°C and 35°C (Figure 7).

Model simulations

We employed the model described under Methods and illustrated in Figure 1 to predict the interaction between Tc and Tsk in control of SkBF. The simulated Tc transients following Tsk changes occurred over a time scale of tens of minutes, not the several minutes seen in Figures 2, 4, and 6, as we expected from the use of a single heat capacity representing the entire body mass. The dynamics of Tes in humans reflect a much smaller thermal mass; revealed in responses to altered thermal balance nearly as rapid as those seen in pulmonary arterial blood temperature (Shiraki et al., 1986). Rather than complicate the model by incorporating fast- and slow-time constant thermal compartments, we focused only on the patterns of change in Tc since the steady-state changes in the single compartment model indicate the changes that would occur more rapidly in the faster thermal compartments.

We ran simulations with A, the constant representing the sensitivity to changes in Tc, set at 2 $liters \cdot min^{-1} \cdot °C^{-1}$, to approximate the values in the literature (Johnson et al., 1979; Wenger et al., 1975; Wyss et al., 1974; Wyss et al., 1975), converted from units of $ml \cdot min^{-1} \cdot 100ml^{-1}$ to $liters \cdot min^{-1}$ with a multiplier of 200, the ratio of a body surface area of 20000 square centimeters to the 50 square cm taken as the surface area of a typical forearm segment of 100 ml volume. We set Tco and Tsko at 36.5°C and 33°C, respectively, to agree with values used by Wyss et al., 1974, 1975. Heat production was set at 1.5 kcal/min. We varied B, the Tsk sensitivity, to obtain various ratios.

With the A:B ratio set at 10, approximating the ratio of sensitivities from the literature (Johnson et al., 1979; Wenger et al., 1975; Wyss et al., 1974; Wyss et al., 1975), the predicted Tc response to a 2°C decline in Tsk from 35°C was a slight decrease, 0.03°C. At higher ratios, the Tc decrement increases. When Tsk sensitivity falls to zero (i.e., all change in SkBF is driven by Tc) the calculated Tc decrement for the Tsk transition from 35°C to 33°C is 0.2°C.

With lower ratios (higher Tsk sensitivity) the amplitude of the Tc change fell, reaching zero at a ratio of 8.3. With still lower ratios, Tc increased with Tsk decrease. For a ratio of 5.3, we obtained a Tes increment of 0.11°C, close to what we observed to accompany decreases in Tsk from 35°C to 33°C.

We also manipulated other parameters of the model, including the reference constants Tco and Tsko. The interactions are complex, reflecting the squared terms and products of Tsk and Tc that occur when equations 2 and 3 are combined. In general, over a range of Tsk, the equilibrium Tc describes a distorted hyperbola with a broad minimum. Over the range of Tsk of this minimum, equilibrium Tc does not change with Tsk. Below that range, Tc increases when Tsk decreases. The absolute value of the dTc/dTsk ratio increases with greater absolute deviation from the minimum point.

DISCUSSION

At least in our setting of uniform temperature over most of the skin, with subjects supine and at rest, the 33°C to 35°C range of Tsk can be regarded as within the thermoregulatory "neutral" or "vasomotor" zone in that Tes is nearly constant at either extreme. Tes changes only one or two tenths of a degree when Tsk is driven from one end of the range to the other. These two degree changes in Tsk have the potential for a large disturbance in thermal balance, since the resultant change in the difference between Tc and Tsk is nearly a factor of two. But the prompt reflex adjustment in SkBF is effective in compensating for the altered gradient. In fact, the adjustment overcompensates, so that Tes rises when Tsk falls and vice versa.

Locally mediated influence of Tsk.

The locally mediated effect of Tsk on SkBF is a potential source of error in the reflex control of thermal balance. The effect, as described by Barcroft and Edholm (1943), is graded over a wide span of skin temperatures, from minimal levels of SkBF at 13°C to maximal levels at temperatures over 42°C that are unexceeded even by the extreme active cutaneous vasodilation that occurs in hyperthermia (Taylor et al., 1984).

We believe that the locally mediated effect of Tsk on FBF is apparent in the experiments (Figure 5) in which we briefly elevated water temperature to 42°C. In the dry arm (on which local Tsk remained 33°C to 39°C), FBF quickly returned to baseline levels when whole-body Tsk was returned to 33°C. In the wet arm on which local Tsk had been near 42°C, return to the levels of FBF associated with 33°C and 35°C Tsk was much slower. We interpret this as another indication of the time-dependent character of the local response, the other side of the well-documented (Barcroft & Edholm, 1943; Brown et al., 1953; Taylor et al., 1984) slow increase after elevation of Tsk.

To the extent that SkBF is influenced by this mechanism in the 33°C to 35°C range, it must progressively influence thermal balance during the development of the effect over a period of tens of minutes. If the reflex SkBF adjustment to a change in Tsk made a perfect adjustment of thermal balance initially, the balance would be disturbed as the local effect developed, requiring correction through the resultant change in Tc.

However, we could see no indication that this was going on. That may be because any tendency for SkBF trend was corrected by reflex response to the resultant change in Tc with small changes in both variables that were not within the resolution of our measurements of FBF and Tes. Also, the local effect of changing Tsk between 33°C and 35°C appears to be small. Brown et al. (1953) found that FBF was nearly the same at 33°C and 35°C, notwithstanding the fact that cooling below 33°C did lower FBF. In the illustration of FBF over the whole range of Tsk studied by Barcroft and Edholm (1943), the relationship appears strongly curved with a relatively low slope in the 33°C to 35°C range. In our experiments, FBF remained nearly

constant when we cycled skin temperature on the forearm only. Although the regression analysis returned a statistically significant coefficient for Tsk, it is only one-sixth of the coefficient representing the reflex influence of Tsk.

On the other hand, we do interpret the difference in FBF levels in the two arms as the consequence of the low local temperature of the dry arm. In terms of a t-test on the overall means, or of the dummy variable analysis, the mean flow on the wet arm in the experiments in which whole-body Tsk was cycled was significantly higher than that of the dry, nearly 1 $ml \cdot min^{-1} \cdot 100ml^{-1}$. The dry arm was approximately 3°C cooler than the average temperature of the wet arm. According to the parameter we calculated for the influence of local temperature, this temperature difference would account for less than 0.3 $ml \cdot min \cdot 100ml^{-1}$, less than half of the actual flow difference, but the slope of the relationship between Tsk and local FBF does appear to be steeper in the range below 33°C.

We recognize that the difference could be connected with handedness -- the wet arm was always the right arm -- and/or with differences in underlying muscle blood flow. Few data on differences between left and right FBF are available. Wenger et al. (1985) found small differences when Tsk was held constant at 33°C in 6 out of 7 subjects tested.

Finally, our regression analyses of the data from the square-wave experiments did yield different coefficients for the two arms, particularly in the analyses limited to the influence of Tsk. Possibly local temperature alters the change in SkBF associated with a given reflex drive. This was suggested by the finding of Barcroft and Edholm (1943) that FBF increase in response to immersion of the feet in hot water was greater with the forearm at 35°C than at 30°C or 32°C.

Reflex influence of Tsk

The coefficients from our regression analysis for the change in FBF per unit change in Tsk are smaller than those reported from studies with subjects who were hyperthermic or exercising (0.3 to 0.5 $ml \cdot min^{-1} \cdot 100ml^{-1} \cdot C^{-1}$ compared to a range in the literature from 0.9 to 1.4 $ml \cdot min^{-1} \cdot 100ml^{-1} \cdot C^{-1}$ (Wenger et al., 1975; Wyss et al., 1974; Wyss et al., 1975). In our study, with the exception of two experiments, Tsk, Tes, and FBF changes were small compared to those

in which Tsk is elevated greatly (often to 40°C or 42°C) and Tes increased 1°C to 2°C. The sensitivity of FBF to Tsk could, of course, be non-linear, with the differential sensitivity lower in our range of Tsk. But when Wyss et al. examined the linearity of the Tsk influence, they found that the coefficient for Tsk was reduced at higher temperatures (Wyss et al, 1975).

A spuriously low estimate of sensitivity to Tsk would be the consequence of ignoring an opposing influence of Tc. When Tsk fell 2°C, FBF decreased by roughly 1 $ml \cdot min^{-1} \cdot 100m^{-1}$, but Tes increased nearly 0.1°C. This change in Tes would correspond to an excitatory influence on FBF near 1 $ml \cdot min^{-1} \cdot 100ml^{-1}$, taking 10 $ml \cdot min^{-1} \cdot 100ml^{-1} \cdot °C^{-1}$ as representative of the values for FBF:Tes sensitivity in the literature (Johnson et al., 1974; Wenger et al., 1975; Wyss et al., 1974; Wyss et al., 1975). Thus, the net decline of 1 $ml \cdot min^{-1} \cdot 100ml^{-1}$ could be seen as the resultant of a positive influence of 1 $ml \cdot min^{-1} \cdot 100ml^{-1}$ associated with Tc combined with a negative influence of 2 $ml \cdot min^{-1} \cdot 100ml^{-1}$. Associating the latter with Tsk would give an estimate for the FBF:Tsk sensitivity double what we calculated.

Reflex influence of Tc

Not only are the parameters we calculated for the FBF:Tes sensitivity smaller than those in the literature, but the one calculated from the wet arm square wave data is negative (Table 1). Naturally, we do not interpret this as indicating that Tc increases cause decreases in SkBF. Rather, this is the spurious mathematical consequence of the small changes in Tes and, possibly, the difference in dynamics between Tes and Tc.

It is true that Tes is not independent of Tsk in that the latter caused changes in the former, but this in itself does not defeat the capability of regression analysis to reveal a reasonable estimate of their respective coefficients. For example, if the "blood flow" data from our simple model are analyzed by the same multiple linear regression procedure, the coefficients A and B in the representation of the reflex control of SkBF (equation 3, methods section) are matched with accuracy to several decimal digits, notwithstanding the fact that the predicted Tc rises when Tsk falls. Of course, if an A:B ratio is selected so that control via Tsk is perfect and Tc does not change at all, then no analytic technique will uncover the correct value for the A parameter.

Our studies with the prolonged period with Tsk at 33°C showed that the upturn in Tes following the transition from 35°C down to 33°C is not a transient that would subside over a longer period of time. The changes that did occur were small, insignificant in the overall averages, and unmatched by changes in FBF that would reveal a high FBF:Tes sensitivity.

We performed the two double-length experiments in part to demonstrate high FBF:Tes sensitivity with Tsk driven out of the neutral zone. These did confirm previous findings, based on regression analysis of the data from the individual experiments (Table 1). Nonetheless, the possibility remains that the differential FBF:Tes sensitivity is non-linear and, in particular, is reduced in the neutral zone.

Dynamics

Tsk dynamics are important in control of the other effectors of thermoregulation. Studies have established that negative rate of change of Tsk is inhibitory to sweating (Libert et al., 1979; McCaffrey et al., 1979; Nadel et al., 1971; Wyss et al., 1974) and excitatory to shivering (Brown & Brengelmann, 1970; Hayward et al., 1977). Within the limits of our time resolution, we could see no indication that rapid changes in Tsk in either direction were influencing the FBF response pattern. Changes in FBF were rapid but appeared to follow Tsk and not to overshoot.

Inverse pattern of Tes versus FBF and Tsk

The inverse relationship between the Tsk and Tes patterns appears surprising at first. We have found no mention of it in the literature except for inverse changes of rectal temperature that Burton and Bazett noticed in their experiments with subjects immersed in water baths (8). But this is the relationship expected on the basis of a simple model incorporating a crude representation of the effects of SkBF changes on heat loss and of Tsk changes on both heat transfer and SkBF (Figure 1).

We do not propose that this model is adequate for predicting the detailed responses of the body to changes in Tsk, even uniform Tsk, nor even the correct time course of changes since it represents the thermal lag of the body through one parameter, whole-body heat capacity. But,

it simplifies thinking about the interaction between blood flow changes driven by changes in Tsk and the thermal consequences of those changes and helps illustrate fundamental points that arise from the assumption that SkBF follows a linear relationship in response to Tc and Tsk.

Specifically, within the neutral zone, i.e., the range of Tsk for a resting person over which control of SkBF suffices for accomplishing thermal balance, a specific equilibrium Tc is associated with each Tsk in a functional relationship. This relationship depends upon not only the sensitivities of SkBF to changes in Tsk and Tc, but also to the other parameters of the control relationship, i.e., the reference constants. For a particular set of parameters, the relationship is a rough hyperbola so that a range of Tsk exists in which no change in Tc follows Tsk changes within this range. Below this range, Tc increases with reduced Tsk.

Without even resorting to a quantitative model, one can see how the incorporation of both Tsk and Tc in control of SkBF can, in the neutral zone, result in an inverse relationship between Tsk and the corresponding equilibrium level of Tc. The response to Tsk is relatively insensitive in terms of $ml \cdot min^{-1} \cdot 100ml^{-1} \cdot °C^{-1}$, but it occurs immediately and immediately affects the convective transfer of heat to the skin. If this results in net thermal balance, then Tc will not change at all. If the balance is not perfect, then Tc will change in the direction to correct SkBF.

If the SkBF sensitivity to Tsk differs from the ideal, i.e., the value for which Tc does not change, then the immediate reflex change in SkBF will over- or under-compensate for the thermal consequences of a change in Tsk. For example, if the actual SkBF:Tsk sensitivity is greater, then the response to falling Tsk would be excessive reduction in SkBF so that Tc would tend to rise toward an eventual equilibrium in which the excessive reduction is corrected by the influence on SkBF of increasing Tc. Extreme SkBF:Tsk sensitivity results in large changes in Tc in the opposite direction of Tsk changes.

With SkBF:Tsk sensitivity below the ideal, SkBF changes in response to Tsk changes are insufficient, so that a corrective change driven by a change in Tc in the same direction is necessary for thermal balance. The extreme is zero sensitivity to Tsk, in which correction of

thermal balance after a change in Tsk must await the development of sufficient negative feedback from the effects on Tc. After a fall in Tsk, Tc will fall and elicit the necessary response of reduced SkBF.

The inverse relationship between Tsk and Tes we observed, therefore, reveals a feedforward design in which the sensitivity of SkBF responses to Tsk in the neutral zone is greater than the optimal level that would result in no Tc change, but not so much so that large inverse changes occur. The expected consequence is a reproducible equilibrium Tc, inversely related to Tsk.

In more commonplace environments than the one in which we maintained Tsk uniform with a water spray, the distribution of Tsk over the body surface is likely to be complex. We presume that the weighing of this information in the reflex control of SkBF results also in overcompensation so that, in the neutral zone, Tc shows an inverse relationship to environmental changes.

Other variables that act to influence SkBF change equilibrium levels of Tc for given environmental conditions within the neutral range. In terms of our model, a change in any one of the parameters, A, B, Tco, Tsko, or SkBFo not only changes the equilibrium Tc for a given Tsk but changes the relationship in terms of the slope and minimum of the Tc:Tsk relationship. For example, with the negative bias (reduced SkBFo) imposed by baroreflex adjustments to assuming the upright posture, a slightly higher equilibrium level for Tc is to be expected (Nielsen et al., 1939). The circadian variation of Tc could be the result of circadian variation of any of these parameters.

CONCLUSION

Our data reveal that the reflex influence of skin temperature on SkBF dominates control of thermal balance in the 33°C to 35°C range of skin temperatures. The immediate change in SkBF that occurs in reflex response to a change in skin temperature results in slight

overcompensation in thermal balance. Consequently, core temperature subsequently moves in the opposite direction, increasing when skin temperature falls and vice versa. A new equilibrium core temperature is established when the resultant feedback influence of core temperature on SkBF corrects the thermal imbalance.

Footnote

1. We reject Webb's "bowl of jello" interpretation of afterdrop (Webb, 1986) as a phenomenon of thermal conduction since the rate of decrease of temperature deep in a cooling solid does not increase when the surface is warmed.

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13. ABSTRACT *(Maximum 200 words)*

In humans, matching of heat loss and heat production in the "neutral" zone, defined operationally in terms of a range of skin temperatures (Tsk), is accomplished by regulation of skin blood flow (SkBF). In four men and four women, we investigated the control of SkBF in this range by setting Tsk at 33°C and 35°C in a square wave pattern (15 min at each temperature) or a step pattern (60 min at 33°C separating short periods at 35°C) by means of water sprayed over the entire body except the head, neck, and one forearm. Forearm blood flow (FBF) followed the pattern of Tsk, both in the forearm in which Tsk followed that of the rest of the body and in the arm exposed to room air (average local Tsk 31.22°C). Esophageal temperature (Tes) rose after Tsk fell and vice versa. This inverse relationship is predicted by a simple one- compartment thermal model in which control of SkBF is simulated as a linear combination of skin and core temperature (Tc). Similar patterns of Tsk applied to only one arm had little influence on FBF. We conclude that the feedforward reflex influence of Tsk on SkBF overcompensates for the effect of Tsk on thermal balance in the neutral zone so that equilibrium Tc has an inverse relationship to Tsk.

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